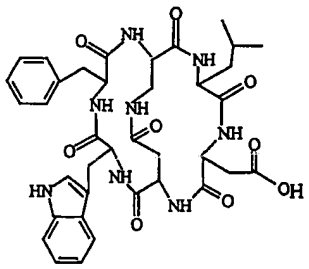
CLAIMS

1. Process for preparing bicyclic peptide compounds of formula (I)

Cyclo(Asp(OH)-Asp-Trp-Phe-Dpr-Leu)

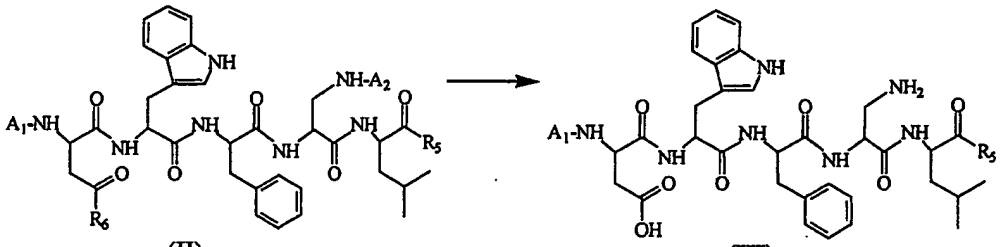


(I)

comprising the following steps:

1) deprotection of the linear pentapeptide of formula (II) in the presence of a solvent to give the compound of formula (III):

A_1-Asp(R_6)-Trp-Phe-Dpr(A_2)-Leu-R_5 A_1-Asp(OH)-Trp-Phe-Dpr(H)-Leu-R_5

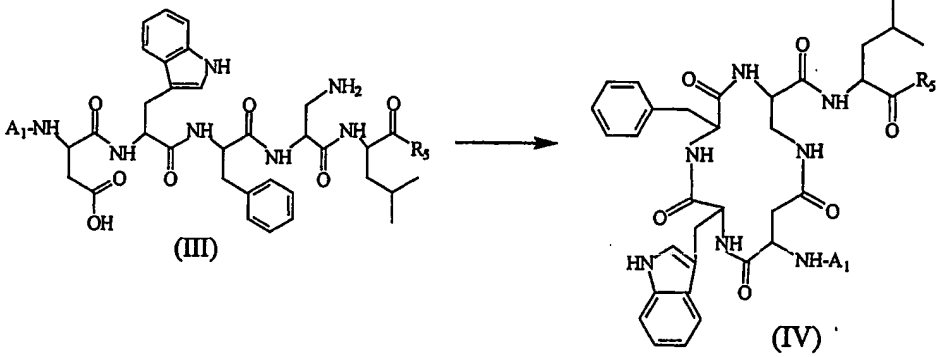


(II) (III)

wherein A_1 and A_2 are two nitrogen protecting groups different from each other, and R_5 and R_6, different from each other, are chosen from benzyloxy and lower alkyloxy groups in which the alkyl part comprises a linear or branched C1-C4 group;

2) intramolecular cyclisation of the compound of formula (III) coming from step 1) in the presence of a solvent and of a suitable coupling agent to give the compound of formula (IV)

A_1-Asp(OH)-Trp-Phe-Dpr(H)-Leu-R_5 → A_1-Asp-Trp-Phe-Dpr-Leu-R_5

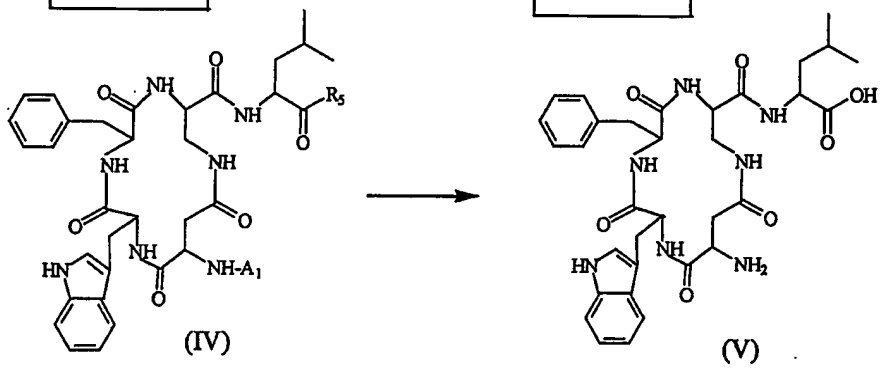


(III) (IV)

wherein R_5 is as defined above;

3) deprotection of the compound of formula (IV) coming from step 2) in the presence of a solvent to give the compound of formula (V)

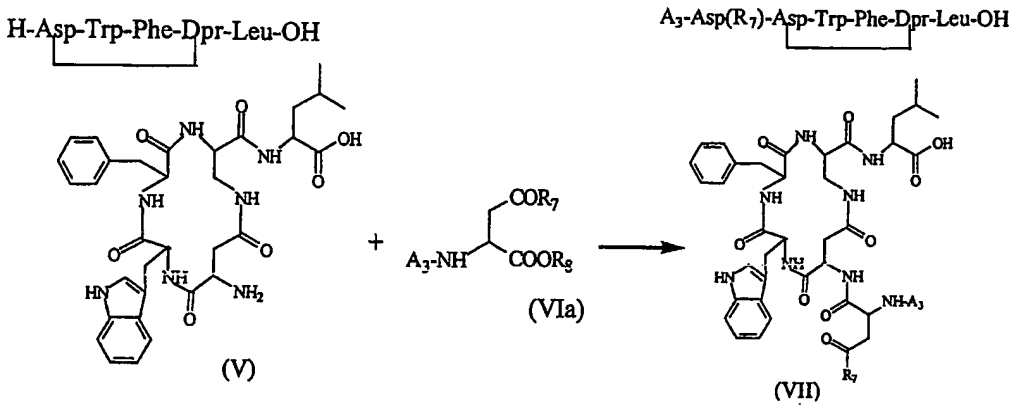
A_1-Asp-Trp-Phe-Dpr-Leu-R_5 → H-Asp-Trp-Phe-Dpr-Leu-OH



(IV) (V)

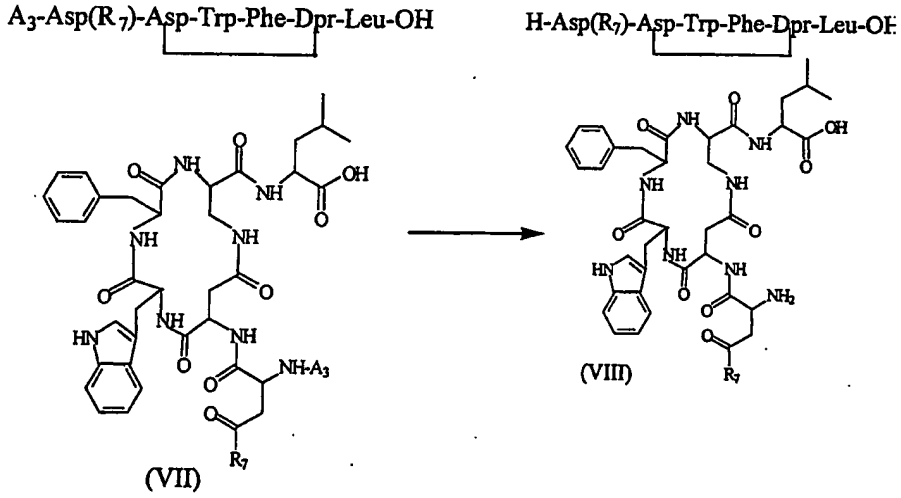
wherein R_5 is as defined above;

4) coupling between the compound of formula (V) coming from step 3) and a protected amino-acid of formula (VIa) in the presence of a solvent, to give compounds of formula (VII)



wherein A_3 is a nitrogen protecting group; R_7 is chosen from benzyloxy and lower alkyloxy groups, in which the alkyl part comprises a linear or branched C1-C4 group; R_8 is a residual group deriving from an activation procedure on the carboxyl group;

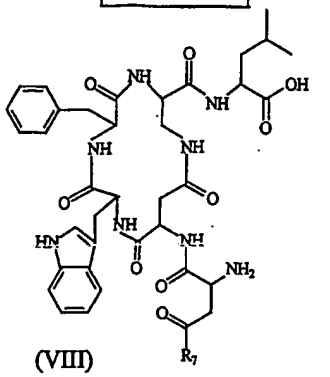
5) deprotection of the compound of formula (VII) coming from step 4) in the presence of a solvent to give a compound of formula (VIII)



wherein R_7 is as defined above;

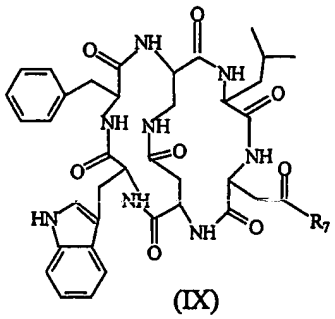
6) intramolecular cyclisation, in the presence of a solvent and of a suitable coupling agent, of the compound of formula (VIII) coming from step 5) to give a bicyclic compound of formula (IX)

H-Asp(R7)-Asp-Trp-Phe-Dpr-Leu-OH



(VIII)

Ciclo(Asp(R 7)-Asp-Trp-Phe-Dpr-Leu)

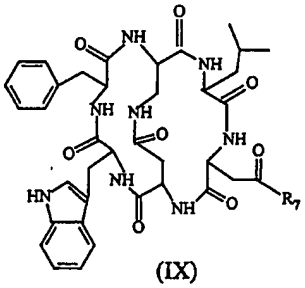


(IX)

wherein R_7 is as defined above;

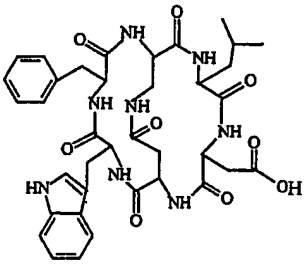
7) deprotection of the bicyclic compound of formula (IX) coming from step 6) in the presence of a solvent, to obtain the compound of formula (I)

Ciclo(Asp(R 7)-Asp-Trp-Phe-Dpr-Leu)



(IX)

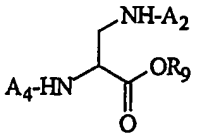
Cyclo(Asp(OH)-Asp-Trp-Phe-Dpr-Leu



(I)

wherein R_7 is as defined above.

2. Process according to claim 1, wherein the linear peptides of formula (II) are obtained by means of a sequential coupling strategy of suitable amino acids starting from a derivative of the amino acid Dpr of formula (X), protected on nitrogen and prepared separately or generated *in situ*



(X)

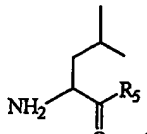
wherein

A_2 and A_4, different from each other, are nitrogen protecting groups;

R_9 is a residual group deriving from an activation procedure, preferably chosen from the group consisting of benzyloxycarbonyl, alkoxycarbonyl comprising a linear or branched C1-C4 group in the alkyl part, and succinimidyl;

according to the following steps:

- reaction of the derivative of formula (X) above reported in the presence of a solvent with a Leu ester of formula (XI)



(XI)

wherein R_5 is defined as in claim 1, to obtain the dipeptide A_4-Dpr(A_2)-Leu-R_5,

- deprotection of the dipeptide A_4-Dpr(A_2)-Leu-R_5, to obtain the monodeprotected dipeptide H-Dpr(A_2)-Leu-R_5;

- coupling the monodeprotected dipeptide H-Dpr(A_2)-Leu-R_5 with the activated ester of the subsequent amino acid Phe and then successively with Trp and Asp, until the compounds of formula (II) are obtained.

3. Process according to claims 1 and 2, wherein the linear peptides of formula (II) are obtained by means of a synthesis strategy comprising the following steps:

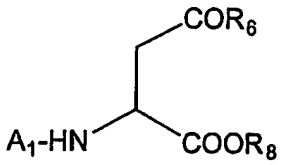
- coupling of the monodeprotected dipeptide H-Dpr(A_2)-Leu-R_5, obtained as described in claim 2, with an activated derivative of the dipeptide of the following formula (XII) A_5-Trp-Phe-OH

(XII)

wherein A_2 and A_5, different from each other, are nitrogen protecting groups, prepared separately or generated *in situ* by coupling an activated ester of a Trp protected on nitrogen prepared separately or generated *in situ*, with a Phe ester and subsequent hydrolysis of the ester group, to obtain the tetrapeptide A_5-Trp-Phe-Dpr(A_2)-Leu-R_5;

- suitable deprotection of the tetrapeptide A_5-Trp-Phe-Dpr(A_2)-Leu-R_5 from the group attached to the nitrogen of Trp;

- coupling of the deprotected tetrapeptide with a compound of formula (VI b)



(VI b)

wherein A_1, R_6 and R_8 are defined as in claim 1.

4. Process according to claims 1-3, wherein the linear peptides of formula (II) are obtained by means of a synthesis strategy of the 3+2 type that involves coupling the tripeptide A_1-Asp(R_6)-Trp-Phe-OH, obtained by removing the nitrogen protecting group from the compounds of formula (XII) above reported, subsequent coupling with a compound of formula (VIb) above reported and then further coupling with the monodeprotected dipeptide H-Dpr-(A_2)-Leu-R_5 prepared as described in claim 2.

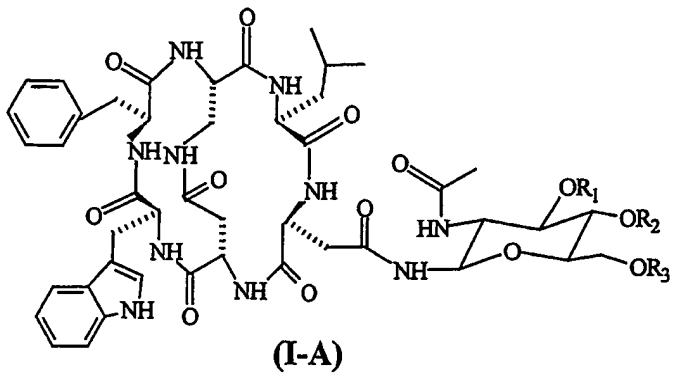
5. Process according to claim 1, wherein said nitrogen protecting groups are selected from the group consisting of benzyloxycarbonyl and alkoxy carbonyls in which the alkyl part comprises a linear or branched C1-C4 group.

6. Process according to claim 5, wherein said nitrogen protecting groups are selected from t-butoxycarbonyl and benzyloxycarbonyl.

7. Process according to claim 1, wherein said R_8 group is selected from the group consisting of benzyloxycarbonyl, alkyloxycarbonyl comprising a linear or branched C1-C4 group in the alkyl part, succinimidyl, benzotriazole possibly substituted by a halogen and azabenzotriazole.

8. Process according to claims 1-7, wherein said linear or branched C1-C4 group is selected from the group consisting of methyl, ethyl, propyl, butyl, isopropyl and t-butyl.

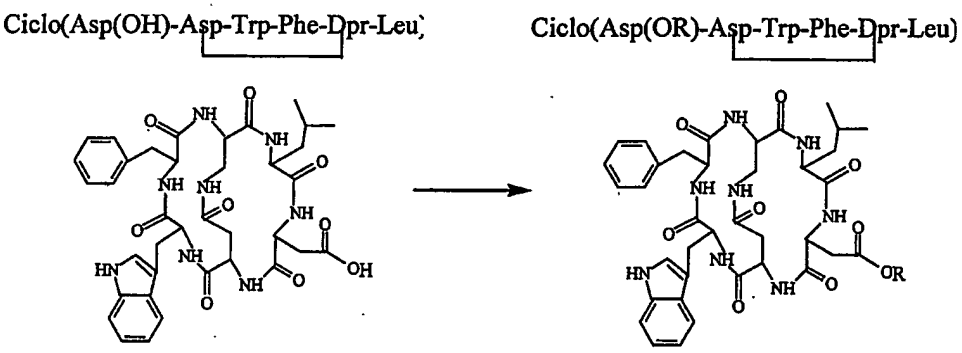
9. Process for preparing a bicyclic glycopeptide compound of formula (I-A)



(I-A)

wherein R_1, R_2 and R_3, equal or different from each other, can be hydrogen or an oxygen protecting group, comprising the following steps:

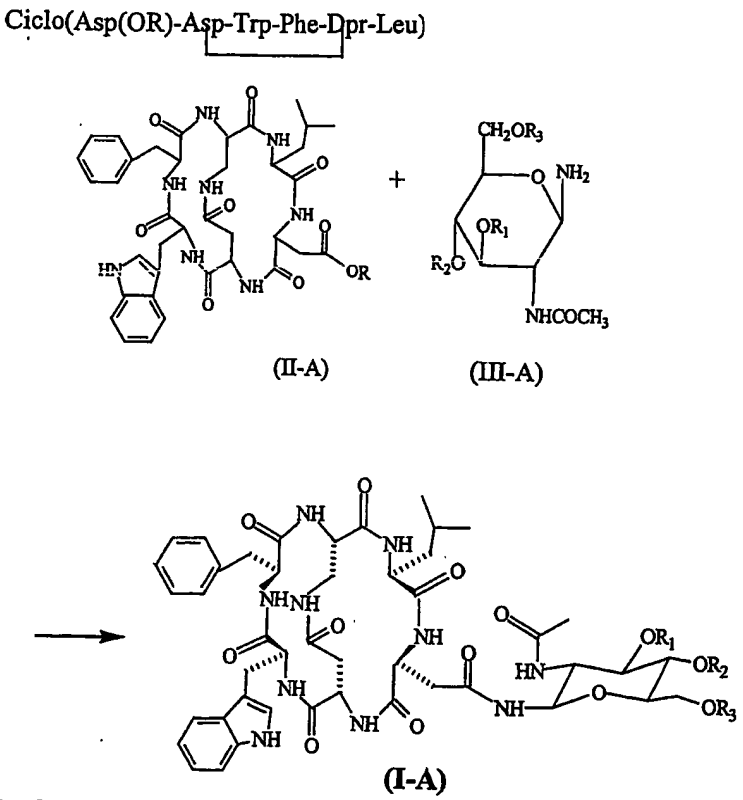
1A) activation of the bicyclic peptide compounds of formula (I) with a suitable coupling agent to obtain a derivative of formula (II-A)



(I) (II-A)

wherein R is a group selected from benzotriazole, possibly substituted with a halogen, azabenzotriazole and succinimidyl;

2A) reaction of the compound of formula (II-A) deriving from step 1A) in the presence of a solvent with the glycosidic derivative of formula (III-A)



wherein R, R_1, R_2, R_3 are defined as above.

10. Process according to claim 9, wherein the compounds of formula (I-A) wherein R_1, R_2 and R_3 are different from H, are transformed into the corresponding compounds of formula (I-A) wherein R_1=R_2=R_3=H, by a deprotection reaction in the presence of a solvent.

11. Process according to claim 9, wherein said oxygen protecting groups are selected from the group consisting of -COR_4 wherein R_4 is a linear or branched C1-C4 alkyl group, phenyl possibly substituted with a halogen atom, benzyl or benzoyl.

12. Process according to claim 11, wherein said C1-C4 alkyl group is selected from the group consisting of methyl, ethyl, propyl, butyl, isopropyl and t-butyl.

13. Process according to claim 12, wherein said C1-C4 alkyl group is methyl.

14. Process according to claim 9, wherein said glycosidic derivatives of formula (III-A) are selected from the group consisting of 2-acetamide-2-deoxy-β-D-

glucopyranosylamine and 2-acetamide-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosylamine.

15. Process according to claim 9, wherein said bicyclic peptide compounds of formula (I) are prepared as described in claim 1.

16. Process according to claims 1 or 9, wherein said coupling agent is selected from the group consisting of isobutyl chloroformate, a carbodiimide possibly in combination with a hydroxyderivative, phosphonium salts, N-oxide guanidine salts and uronium salts.

17. Process according to claim 16, wherein said carbodiimides are selected from dicyclohexylcarbodiimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; said hydroxyderivative is selected from 1-hydroxybenzotriazole, 6-chloro-1-hydroxybenzotriazole, hydroxysuccinimide and 1-hydroxy-7-azabenzotriazole; said phosphonium salts, N-oxide guanidine salts and uronium salts are selected from (Benzotriazol-1-yloxy)tri(dimethylamino)phosphonium hexafluorophosphate, (Benzotriazol-1-yloxy)tripyrrolidine phosphonium hexafluorophosphate, 1-[bis(dimethylamino)methylene]-1H-benzotriazolium-3-oxide hexafluorophosphate, 1-[bis(dimethylamino)methylene]-5-chloro-1H-benzotriazolium-3-oxide hexafluorophosphate, 1-[bis(dimethylamino)methylene]-1H-benzotriazolium-3-oxide tetrafluoroborate, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazole[4,5-b]pyridinium-3-oxide hexafluorophosphate, 1-[bis(dimethylamino)methylene]-5-chloro-1H-benzotriazolium-3-oxide tetrafluoroborate, O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate, O-(bicyclo[2.2.1]hept-5-ene-2,3-dicarboximido)-N,N,N',N'-tetramethyluronium tetrafluoroborate, and O-(N-succinimidyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate.

18. Process according to claims 1 or 9, wherein said coupling reactions are carried out in the presence of a tertiary amine in an organic solvent at a temperature comprised between –20 and +50°C.

19. Process according to claim 18, wherein said tertiary amine is selected from the group consisting of N-methylmorpholine, triethylamine and diisopropylethylamine, and said organic solvent is selected from the group consisting of ethyl acetate, dimethylformamide and N-methylpyrrolidone.

20. Process according to claims 1 or 10, wherein said deprotection reactions are carried out by means of hydrogenation in the presence of a catalyst in a solvent selected from solvents which dissolve the components of the reaction without reacting with them, excluding ketones and solvents which poison the catalyst, at a temperature comprised between –20 and +50°C.

21. Process according to claim 20, wherein said catalyst is selected from 5% and 10% Palladium and said solvent is selected from dimethylformamide, N-methylpyrrolidone, acetic acid, p-toluenesulfonic acid, methanol, ethanol, isopropanol, and mixtures thereof.

22. Process according to claims 1 or 10, wherein said deprotection reactions are carried out by means of acid treatment with pure acids or with acids mixed with other solvents, at a temperature comprised between –20 and +50°C.

23 Process according to claim 22, wherein said acids are selected from hydrochloric acid, trifluoroacetic acid and formic acid.

24. Process according to claims 1 or 10, wherein said deprotection reactions are carried out by means of treatment with a base compound in the presence of a solvent, at a temperature comprised between –20 and +50°C.

25. Process according to claim 24, wherein said base compound is selected from hydroxides of alkali metals or alkaline earth metals, and said solvent is selected from the group consisting of water, dioxane, acetonitrile, methanol, ethanol, isopropanol, and mixtures thereof.